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EXAMINER	
WOODWARD, CHERIE MICHELLE	
ART UNIT	**PAPER NUMBER**
1647	

DATE MAILED: 05/10/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/502,344	ROSS ET AL.	
	Examiner	Art Unit	
	Cherie M. Woodward	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 March 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-38 and 43-46* is/are pending in the application.

4a) Of the above claim(s) *17,44 and 46* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-16, 18-38, 43, and 45* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *23 July 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *11 May 2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group I, claims 1-38, 43, and 45, and SEQ ID NO: 18 (human growth hormone - hGH) in the replies filed on 30 November 2005 and 8 March 2006 are acknowledged. The traversal is on the grounds that the claims should not be restricted because the claims contain the special technical feature of a construct comprising more than two ligand receptor binding domains of a cytokine ligand. This is not found persuasive because claims 1-38, 43, and 45 (Group I) are drawn to a polypeptide, a nucleic acid encoding the polypeptide, a vector comprising the nucleic acid, a cell transformed with the vector, a method of making the polypeptide, and a method of using the polypeptide. Claims 44 and 46 (Group II) are drawn to a pharmaceutical composition comprising the nucleic acid molecule and a method for treating a disease. Unity of invention was found lacking because the special technical feature of Group I is the polypeptide, which is not required in claims 44 or 46.

37 CFR 1.475 discusses Unity of Invention during the national stage. According to 37 CFR 1.475(d), if multiple products, processes of manufacture or uses are claimed, the first invention of the category first mentioned in the claims of the application and the first recited invention of each of the other categories related thereto will be considered as the main invention in the claims, see PCT Article 17(3)(a) and 37 CFR 1.476(c). Thus, the polypeptide of SEQ ID NO: 18 (growth hormone), the nucleic acid encoding it, the vector, transformed host cell, the first method of making, and the first method of using the polypeptide have been grouped together for purposes of restriction in this national stage application.

The requirement is still deemed proper and is therefore made FINAL.

Formal Matters

2. Claims 1-38 and 43-46 are pending. Claims 17, 44, and 46 have been withdrawn from consideration as to a non-elected invention. Claims 1-16, 18-38, 43, and 45 are under examination.

Information Disclosure Statement

3. The information disclosure statement (IDS) submitted on 11 May 2005 has been considered, in part. A signed copy is attached hereto. Items that have been lined-through have not been considered because they are not in English and no translation was provided. Applicant is advised that the date of any re-submission of any item of information contained in this information disclosure statement or the submission of any missing elements will be the date of submission for purposes of determining

compliance with the requirements based on the time of filing the statement, including all certification requirements for statements under 37 CFR 1.97(e). See MPEP § 609.05(a).

Applicant's attention is also drawn to reference "AJ," which contains a typographical error. Nadine S. Welch should be Nadine Weich. This reference has been considered.

Specification

4. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

The following title is suggested: Human growth hormone tandem fusion proteins.

Provisional Obviousness-Type Double Patenting Rejection

5. Claims 1, 18-24, 29, 30-31, 34-36, 38, 43, and 45 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 43, 53-57, 64-66, and 69-81 of copending Application No. 10/311,473. Although the conflicting claims are not identical, they are not patentably distinct from each other because instant claim 1 contains the same subject matter as claim 43. Instant claims 18 and 19 contain the same subject matter as claim 53. Instant claims 20 and 21 contain the same subject matter as claim 54. Instant claim 22 contains the same subject matter as claim 55. Instant claim 23 contains the same subject matter as claim 56. Instant claim 24 contains the same subject matter as claim 57. Instant claim 29 contains the same subject matter as claim 64. Instant claim 34 contains the same subject matter as claims 69 and 70. Instant claim 35 contains the same subject matter as claims 71-73. Instant claim 36 contains the same subject matter as claim 74. Instant claim 38 contains the same subject matter as claims 75-79. Instant claim 43 contains the same subject matter as claim 80. Instant claim 45 contains the same subject matter as claim 45.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

6. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct

from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claim Rejections - 35 USC § 101

7. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

8. Claims 1-16, 18-29, 32-38, 43, and 45 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. The claims are drawn to a polypeptide comprising more than two ligand receptor binding domains of a cytokine ligand and a linker, where the linker comprises at least one proteolytic cleavage site. Page six of the specification gives various examples of types of linkage between the multiple ligand binding domains of a cytokine receptor, but does not limit the linkage to any particular type. Therefore, the linkage includes non-covalent interactions between two proteins that bind to each other. Oligomers of human growth hormone (hGH) are found naturally in plasma. These oligomers are known in the art as "big" and "big-big" growth hormone (see, for example, Stolar et al., J Clin Endocrin and Metabol 1984 59(2):212-218, see especially Abstract). It is well known that a single molecule of growth hormone naturally associates with two identical receptor molecules and that this occurs through two unique receptor-binding sites on GH and a common binding pocket on the extracellular domain of two receptors. Additionally, Zinc binds to human growth hormone and induces hGH to dimerize naturally (see i.e. Cunningham et al., Science 1991 Aug 2 253(5019):545-548; see

specifically p. 547 column 1, last paragraph to column 2, first paragraph) (see also, Wright et al., J Clin Invest Nov 1974 54:1064-1073, especially p. 1064, Abstract, discussing covalent and non-covalent linkages in multimers of "big" and "little" human growth hormone). As such, the claims are drawn to products of nature and products of nature are non-statutory subject matter.

Claims 29, and 32-38 are drawn to a nucleic acid encoding a polypeptide of claim 1 or a sequence that hybridizes to it and which has cytokine receptor modulating activity and the polypeptide encoded by the nucleic acid according to claim 29. Claim 29 is drawn to a nucleic acid encoding a polypeptide of claim 1. The polypeptide of claim 1 is not limited to a polypeptide wherein the linkage is a fusion protein. Therefore, claims 29 and 30 encompass nucleic acids that encode two discrete proteins (one comprising growth hormone and one comprising the extracellular domain of growth hormone receptor, the second one could be either GHBP or membrane-bound growth hormone) that form the claimed polypeptide. Claim 32 is drawn to a polypeptide encoded by the nucleic acid molecule of claim 29 and therefore encompasses a discrete protein, such as growth hormone. Like the aforementioned claims, the claims are not drawn to an isolated polypeptide, and therefore the claim encompasses growth hormone as found in the human body, which is a product of nature. Products of nature are non-statutory subject matter.

Claim 33 is drawn to a polypeptide of claim 32 that is modified by deletion, addition, or substitution of at least one amino acid residue. The polypeptide of claim 33 encompasses the naturally occurring membrane-bound growth hormone, which comprises the extracellular domain of growth hormone receptor. There is no upper limit placed on the number of residues that can be modified in the polypeptide of claim 33. Therefore, claim 33 encompasses a naturally occurring polypeptide which is an alternative splice variant, peptides produced from naturally occurring single nucleotide polymorphisms, or one in which the signal sequence is cleaved. The claim is not drawn to an isolated polypeptide, and therefore the claim encompasses GHBP as found in the human body, which is a product of nature, and as such, is non-statutory subject matter.

Claim Rejections - 35 USC § 112, First Paragraph

Enablement

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 38 and 45 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claims contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is undue include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability, 5) existence of working samples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

Claim 38 is drawn to a cell transformed/transfected with a vector comprising the nucleic acid of claim 29. Mammalian cells are contemplated by the invention (see specification p. 10, paragraph 0059). As such, the specification does not teach how to make or use transgenic animals. However, an amendment to insert the word "isolated" would be remedial.

Claim 45 is drawn to a method for treating a disease selected from the group consisting of GH deficiency, as elected. The specification fails to teach how to use the polypeptide of the invention to treat GH deficiency. The specification briefly discusses that disorders of acromegaly and gigantism result from an excess of growth hormone, usually due to pituitary tumors (p. 2, paragraph 0008). The specification also mentions that a drug currently under trial is the pegylated GH antagonist 82036 (p. 2, paragraph 0008). Additionally, the specification teaches modes of administering the polypeptide on page 11. However, the specification fails to teach the method or any steps of a method for treating GH deficiency using the claimed polypeptide.

The specification has not provided the person of ordinary skill in the art the guidance necessary to be able to make and use a transgenic animal or use the polypeptide in a method of treating GH deficiency. Due to the large quantity of experimentation necessary to determine how to use the polypeptides to treat GH deficiency, the lack of direction/guidance presented in the specification regarding same, the lack of working examples, and the teachings of the prior art and the complex nature of the invention, undue experimentation would be required of the skilled artisan to use the claimed invention.

11. Claims 30 and 31 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claims contains subject matter which was not described in the specification

in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claim 30 recites a nucleic acid molecule comprising the sequence selected from the group consisting of a sequence which hybridizes to the sequence of (i) above and which has cytokine receptor modulating activity. Claim 31 recites a nucleic acid molecule which hybridizes under stringent hybridization conditions to the sequence represented by a growth hormone DNA.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is undue include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability, 5) existence of working samples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

There is no teaching in the claims or the specification to the length of a complementary nucleic acid sequence that could bind to the claimed nucleic acid, such that the claimed nucleic acid would hybridize. Applicant has not taught the length of the sequence envisioned for hybridizing. Additionally, the specification fails to recite the conditions of hybridization. It is well known in the art that the stringency of hybridization is dictated by wash and salt concentration.

Due to the large quantity of experimentation necessary to generate the thousands of hybridizing nucleic acids recited in the claim, the lack of direction/guidance presented in the specification regarding the nucleic acids that are to hybridize with the complementary nucleic acid, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes that washing and salt concentration determine the stringency of hybridization, and the breadth of the claims which fail to recite any limitations as to the length of the nucleic acids that are to hybridize with the complementary nucleic acid, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Claim Rejections - 35 USC § 112, First Paragraph

Scope of Enablement

12. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

13. Claims 1-16, 18-29, 32-38, 43, and 45 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated polypeptide construct consisting of two growth hormone ligand tandem polypeptides linked together by a thrombin-cleavable linker, does not reasonably provide enablement for all polypeptides, including fusion proteins, comprising more than two ligand receptor binding domains of a cytokine ligand and a linker. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is undue include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability, 5) existence of working samples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The claims recite a polypeptide comprising more than two ligand receptor binding domains of a cytokine ligand, linked by a linker molecule, wherein the linker molecule comprises at least one proteolytic cleavage site; wherein the cleavage site is sensitive to a serum protease; wherein the serum protease is thrombin; wherein the cleavage site comprises SEQ ID NO: 1 or a variant thereof; wherein the cleavage site comprises SEQ ID NO: 2 or a variant thereof; wherein the cleavage site comprises SEQ ID NO: 3; wherein the cleavage site comprises SEQ ID NO: 4 or a variant thereof; wherein the cleavage site comprises a center and two copies of SEQ ID NO: 2 or a variant thereof, which flank the center of said cleavage site; wherein the polypeptide comprises at least four receptor binding domains; wherein the polypeptide comprises 3,4,5,6,7,8,9, or 10 receptor binding domains; wherein the polypeptide comprises greater than 10 receptor binding domains; wherein the polypeptide is an antagonist to the cytokine; wherein the polypeptide is an agonist to the cytokine; wherein the receptor binding domain is the receptor binding domain selected from the group of growth hormone [as elected]; wherein the binding domain is the receptor binding domain of growth hormone; wherein the linker is a polypeptide which comprises from 5 to 50 amino acid residues; wherein the linker comprises from 5 to 30 amino acid residues; wherein the linker comprises at least one copy of SEQ ID NO: 6; wherein the linker is 5 amino acids in length and consists of two copies of SEQ ID NO: 6; wherein the linker is 10 amino acids in length and consists of two copies of SEQ ID NO: 6; wherein the linker is 15 amino acids in length and consists of three copies of SEQ ID NO: 6; wherein the linker is 20 amino acids in length and consists of four copies of SEQ ID NO: 6; wherein the polypeptide is a fusion protein comprising inframe translational fusions of ligand

binding domains; a polypeptide according to claim 1 comprising chemical crosslinkers wherein the chemical crosslinkers serve to link the ligand binding domains; wherein the chemical crosslinker comprises a homo-bifunctional corsslinker selected from the group consisting of disuccinimidyl-suberimidate-dihydrochloride, dimethyl-adipimidate-dihydrochloride, and 1,5,-2,4 dinitrobenzene; wherein the crosslinker comprises a hetero-bifunctional crosslinker selected from the group consisting of N-hydroxysuccinimidyl 2, 3-dibromopropionate; 1-ethyl-3-[3-dimethylaminopropyl] carbodiimide hydrochloride; and succinimidyl 4-[n-maleimidomethyl]-cyclohexane-1-carboxylate; a nucleic acid molecule comprising a nucleic acid sequence which encodes a polypeptide according to claim 1; a polypeptide encoded by the nucleic acid molecule according to claim 29; a polypeptide according to claim 32 wherein said polypeptide is modified by deletion, addition, and/or substitution of at least one amino acid residue and said modification enhances the antagonistic or agonistic effects of said polypeptide with respect to the inhibition or activation of receptor mediated cell signaling; a vector comprising the nucleic acid molecule of claim 29; a vector according to claim 34 wherein the vector is an expression vector adapted for prokaryotic or eukaryotic gene expression; a vector according to claim 34 wherein the vector further encodes a secretion signal linked to the polypeptide to facilitate purification of the polypeptide; a method to prepare a polypeptide according to claim 1 comprising (i) growing a cell transformed or transfected with a nucleic acid of claim 29 in conditions conducive to the manufacture of the polypeptide and (ii) purifying the polypeptide from the cell or its growth environment; a cell transformed/transfected with the vector of the nucleic acid of claim 29; a pharmaceutical composition comprising the polypeptide of claim 1 and a pharmaceutically acceptable carrier, excipient, or a diluent; a method for treating a disease selected from the group consisting of: GH deficiency [as elected], wherein said method comprising administering to a patient in need thereof a pharmaceutical composition according to claim 43.

The nature of the invention is a human growth hormone tandem/dimer comprising two hGH ligands that are linked together, nucleic acid vectors, host cells encoding the polypeptide linked proteins, a pharmaceutical composition comprising the hGH tandem/dimer polypeptide and a method of treating a disease using the hGH polypeptide pharmaceutical composition. The breadth of claim 1 is such that it encompasses any polypeptide comprising more than two receptor-binding domains of a cytokine ligand. The linkage between these two parts is not limited by the specification to any particular non-covalent or covalent embodiments. The sole recited characteristic of the linker in claim 1 is that it comprise at least one proteolyic cleavage site. The cytokine, or ligand-binding domain of a cytokine, is not limited to a native sequence of a cytokine and therefore encompasses cytokines with one or more variations to the

native sequence. Claims 4-8 and 18-24 provide various limitations on the type of linker and/or number of copies. Claims 26 –28 limit the linkers to chemical crosslinkers. Claim 25 limits the claimed polypeptide to a fusion protein.

With respect to covalently bound ligands and receptors, the prior art teaches cytokines and soluble receptors bound by chemical cross-linking. While other non-covalently bound cytokine-soluble receptor pairs can act as an antagonist or an agonist depending on the conditions examined, it is not predictable that a covalently bound pair, such a fusion protein, that acts antagonistically when non-covalently bound, could act as an agonist when covalently bound. As described in teachings of Fernandez-Botran et al., (Expert Opin Biol Ther. 2002 Aug; 246(2): 585-605 Review), release of the bound cytokine is necessary in order for the complex to act agonistically and therefore the covalent bonding would preclude in vivo agonistic effects. The subclass of receptors that includes growth hormone requires dimerization of two membrane-bound receptors for activation of the receptor, and the covalently bound binding agent would act to prevent dimerization of these receptors.

While Applicants have shown that a fusion of two growth hormone ligands, each of which contains two growth hormone receptor binding domains, meet the limitations of the claimed invention, Applicants have not provided any teaching in the specification of antagonistic or agonist activities of other polypeptides comprising more than two receptor binding domains of a cytokine ligand. Thus the specification fails to teach the skilled artisan how to use the full range of polypeptides with more than two ligand-binding domains, as claimed. The specification has not provided the person of ordinary skill in the art the guidance necessary to be able to use such a polypeptide for the claimed use. Due to the large quantity of experimentation necessary to determine if such polypeptides could be used as agonists or antagonists, the unpredictability in determining whether such a polypeptide could be used as an agonist or antagonist, the lack of direction/guidance presented in the specification regarding same, the lack of working examples of other polypeptides, and the teachings of the prior art and the complex nature of the invention, undue experimentation would be required of the skilled artisan to use the claimed invention.

Claim Rejections - 35 USC § 112, First Paragraph
Written Description

14. Claims 1-16, 18-38, 43, and 45 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. This is a

written description rejection, rather than an enablement rejection under 35 U.S.C. 112, first paragraph. Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

The claims recite a polypeptide comprising more than two ligand receptor binding domains of a cytokine ligand, linked by a linker molecule, wherein the linker molecule comprises at least one proteolytic cleavage site; wherein the cleavage site is sensitive to a serum protease; wherein the serum protease is thrombin; wherein the cleavage site comprises SEQ ID NO: 1 or a variant thereof; wherein the cleavage site comprises SEQ ID NO: 2 or a variant thereof; wherein the cleavage site comprises SEQ ID NO: 3; wherein the cleavage site comprises SEQ ID NO: 4 or a variant thereof; wherein the cleavage site comprises a center and two copies of SEQ ID NO: 2 or a variant thereof, which flank the center of said cleavage site; wherein the polypeptide comprises at least four receptor binding domains; wherein the polypeptide comprises 3,4,5,6,7,8,9, or 10 receptor binding domains; wherein the polypeptide comprises greater than 10 receptor binding domains; wherein the polypeptide is an antagonist to the cytokine; wherein the polypeptide is an agonist to the cytokine; wherein the receptor binding domain is the receptor binding domain selected from the group of growth hormone [as elected]; wherein the binding domain is the receptor binding domain of growth hormone; wherein the linker is a polypeptide which comprises from 5 to 50 amino acid residues; wherein the linker comprises from 5 to 30 amino acid residues; wherein the linker comprises at least one copy of SEQ ID NO: 6; wherein the linker is 5 amino acids in length and consists of two copies of SEQ ID NO: 6; wherein the linker is 10 amino acids in length and consists of two copies of SEQ ID NO: 6; wherein the linker is 15 amino acids in length and consists of three copies of SEQ ID NO: 6; wherein the linker is 20 amino acids in length and consists of four copies of SEQ ID NO: 6; wherein the polypeptide is a fusion protein comprising inframe translational fusions of ligand binding domains; a polypeptide according to claim 1 comprising chemical crosslinkers wherein the chemical crosslinkers serve to link the ligand binding domains; wherein the chemical crosslinker comprises a homo-bifunctional corsslinker selected from the group consisting of disuccinimidyl-suberimidate-dihydrochloride, dimethyl-adipimidate-dihydrochloride, and 1,5,-2,4 dinitrobenzene; wherein the crosslinker comprises a hetero-bifunctional crosslinker selected from the group consisting of N-hydroxysuccinimidyl 2, 3-dibromopropionate; 1-ethyl-3-[3-dimethylaminopropyl] carbodiimide hydrochloride; and succinimidyl 4-[n-maleimidomethyl]-cyclohexane-1-carboxylate; a nucleic acid molecule comprising a nucleic acid sequence which encodes a polypeptide according to claim 1; a polypeptide encoded by the nucleic acid molecule according to claim 29; a polypeptide according to

claim 32 wherein said polypeptide is modified by deletion, addition, and/or substitution of at least one amino acid residue and said modification enhances the antagonistic or agonistic effects of said polypeptide with respect to the inhibition or activation of receptor mediated cell signaling; a vector comprising the nucleic acid molecule of claim 29; a vector according to claim 34 wherein the vector is an expression vector adapted for prokaryotic or eukaryotic gene expression; a vector according to claim 34 wherein the vector further encodes a secretion signal linked to the polypeptide to facilitate purification of the polypeptide; a method to prepare a polypeptide according to claim 1 comprising (i) growing a cell transformed or transfected with a nucleic acid of claim 29 in conditions conducive to the manufacture of the polypeptide and (ii) purifying the polypeptide from the cell or its growth environment; a cell transformed/transfected with the vector of the nucleic acid of claim 29; a pharmaceutical composition comprising the polypeptide of claim 1 and a pharmaceutically acceptable carrier, excipient, or a diluent; a method for treating a disease selected from the group consisting of: GH deficiency [as elected], wherein said method comprising administering to a patient in need thereof a pharmaceutical composition according to claim 43.

Vas-Cath Inc. V. Mahurkar, 19 USPQ2d 1111, states that Applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention, for purposes of the written description inquiry, is whatever is now claimed (see page 1117). A review of the language of the claim indicates that these claims are drawn to a genus, i.e., a polypeptide comprising more than two cytokine receptor binding domains of a cytokine ligand, linked by a linker molecule, wherein the linker molecule comprises at least one proteolytic cleavage site. Additionally, variants of the cleavage site are also encompassed within the genus.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof.

A description of a genus may be achieved by means of a recitation of a representative number of species falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus. *Regents of the University of California v. Eli Lilly & Co.*, 119 F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). In *Regents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412), the court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide

an adequate written description of the genus. The court indicated that, while applicants are not required to disclose every species encompassed by a genus, the description of the genus is achieved by the recitation of a representative number of species falling within the scope of the claimed genus. At section B(1), the court states, "An adequate written description of a DNA ... requires a precise definition, such as by structure, formula, chemical name, or physical properties, not a mere wish or plan for obtaining the claimed chemical invention."

There is a single species of the claimed genus disclosed that is within the scope of the claimed genus, *i.e.* a hGH tandem/dimer protein. The disclosure of a single disclosed species may provide an adequate written description of a genus when the species disclosed is representative of the genus. However, the present claim encompasses numerous species that are not further described. Applicant has not adequately described other polypeptides comprising more than two cytokine receptor binding domains of a cytokine ligand, linked by a linker molecule, wherein the linker molecule comprises at least one proteolytic cleavage site, in humans or in any other species. Applicants have not adequately described proteins meeting the limitations of the claims.

With respect to fusion proteins comprising inframe translational fusions of ligand binding domains, the specification fails to provide any description of generic ligand binding domains such that the skilled artisan would know that they were in possession of the claimed invention.

One of skill in the art would not recognize from the disclosure that the applicant was in possession of the genus. The specification does not clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed (see *Vas-Cath* at page 1116).

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision (see page 1115).

Claim Rejections - 35 USC § 112, Second Paragraph

15. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

16. Claims 29 and 32-38 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 29 is drawn to nucleic acid sequences that encode a polypeptide ligand binding domains of a cytokine receptor comprising more than two parts. These two or more proteins could be encoded by a

single nucleic acid, however, it is not clear which of these two (or more) proteins is being referred to by the phrase "a polypeptide" of claim 1. The remaining claims are rejected for depending from an indefinite claim.

17. Claims 13 and 14 recites the limitation "said cytokine". There is insufficient antecedent basis for this limitation in the claim.

18. A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. See MPEP § 2173.05(c). Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949). In the present instance, claim 15 recites the broad recitation "interleukins" (line 4), and the claim also recites IL-2 (line 5) which is the narrower statement of the range/limitation.

19. Claims 30 and 31 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 30 recites a nucleic acid molecule comprising the sequence selected from the group consisting of a sequence which hybridizes to the sequence of (i) above and which has cytokine receptor modulating activity. Claim 31 recites a nucleic acid molecule which hybridizes under stringent hybridization conditions to the sequence represented by a growth hormone DNA. The term "hybridizes" is indefinite as the conditions of hybridization are not set forth. Similarly, the phrase "stringent hybridization conditions" is indefinite, as the specification fails to set forth the metes and bounds of the stringent conditions.

20. Claims 2-30, 32-33 and 35-36 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant

regards as the invention. the "A" in the dependent claims should be "The". Otherwise, the claim connotes that there is more than one polypeptide of claim 1, for example. Also, claim 30, (i) has "a" where it should have "the" in the first line.

21. Claim 33 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 33 is indefinite as the standard against which one measures the antagonistic or agonistic effects are not set forth.

Claim Rejections - 35 USC § 102

22. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

23. Claims 1, 13, and 43 are rejected under 35 U.S.C. 102(b) as being anticipated by Baumann et al., (1989, Metabolism, 38(4): 330-333).

The claims recite a polypeptide comprising more than two receptor binding domains of a cytokine ligand, linked by a linker molecule, wherein the linker molecule comprises at least one proteolytic cleavage site; wherein the polypeptide is an antagonist to the cytokine; a pharmaceutical composition comprising the polypeptide of claim 1 and a pharmaceutically acceptable carrier, excipient, or a diluent.

Baumann et al., teaches a covalently cross-linked complex of growth hormone and the growth hormone binding protein linked through a covalent chemical cross-linker (p. 330, Materials and Methods). This polypeptide complex would prevent dimerization of membrane-bound growth hormone receptor and is therefore inherently an antagonist of growth hormone receptor. The polypeptide was injected into rats in a pharmaceutical composition.

24. Claims 1, 13-14, and 43 are rejected under 35 U.S.C. 102(b) as being anticipated by Cunningham et al., (US Patent 5,506,107, 9 April 1996).

The claims recite a polypeptide comprising more than two receptor binding domains of a cytokine ligand, linked by a linker molecule, wherein the linker molecule comprises at least one proteolytic cleavage site; wherein the polypeptide is an antagonist to the cytokine wherein the polypeptide is an

agonist to the cytokine; wherein said method comprising administering to a patient in need thereof a pharmaceutical composition according to claim 43.

Cunningham et al., teach ternary complexes of hGH with their receptors that can act as agonists or antagonists. Agonists comprised of hGH ligands are taught at column 3, lines 36-67 to column 4, lines 1-5. hGH-C-terminal-fusion proteins are taught at column 36, Example 9. Antagonists comprised of hGH ligands are taught at column 8, lines 47-65. Antagonist and agonist ligand variants are taught at column 23, lines 34-52. Therapeutic compositions are taught at column 22, lines 10-67.

Claim Rejections - 35 USC § 103

25. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

26. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

27. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

28. Claims 1,5,7-8,18-24, 29, 32-36, and 38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cunningham et al., (US Patent 5,506,107, 9 April 1996) and Baumann et al., (1989,

Metabolism, 38(4): 330-333), in view of Sytkowski et al., (WO 99/02710, published January 21, 1999), in further view of Desplancq et al., (Protein Engineering 1994 7(8):1027-1033).

The claims recite a polypeptide comprising more than two ligand binding domains of a cytokine receptor, linked by a linker molecule, wherein the linker molecule comprises at least one proteolytic cleavage site; wherein the cleavage site is sensitive to a serum protease; wherein the serum protease is thrombin; wherein the cleavage site comprises SEQ ID NO: 1 or a variant thereof; wherein the cleavage site comprises SEQ ID NO: 2 or a variant thereof; wherein the cleavage site comprises SEQ ID NO: 3; wherein the cleavage site comprises SEQ ID NO: 4 or a variant thereof; wherein the cleavage site comprises a center and two copies of SEQ ID NO: 2 or a variant thereof, which flank the center of said cleavage site; wherein the polypeptide comprises at least four ligand binding domains; wherein the polypeptide comprises 3,4,5,6,7,8,9, or 10 ligand binding domains; wherein the polypeptide comprises greater than 10 ligand binding domains; wherein the polypeptide is an antagonist to the cytokine; wherein the polypeptide is an agonist to the cytokine; wherein the cytokine receptor ligand binding domain is the ligand binding domain selected from the group of growth hormone [as elected]; wherein the binding domain is the binding domain of growth hormone; wherein the linker is a polypeptide which comprises from 5 to 50 amino acid residues; wherein the linker comprises from 5 to 30 amino acid residues; wherein the linker comprises at least one copy of SEQ ID NO: 6; wherein the linker is 5 amino acids in length and consists of two copies of SEQ ID NO: 6; wherein the linker is 10 amino acids in length and consists of two copies of SEQ ID NO: 6; wherein the linker is 15 amino acids in length and consists of three copies of SEQ ID NO: 6; wherein the linker is 20 amino acids in length and consists of four copies of SEQ ID NO: 6; wherein the polypeptide is a fusion protein comprising inframe translational fusions of ligand binding domains; a polypeptide according to claim 1 comprising chemical crosslinkers wherein the chemical crosslinkers serve to link the ligand binding domains; wherein the chemical crosslinker comprises a homo-bifunctional corsslinker selected from the group consisting of disuccinimidyl-suberimidate-dihydrochloride, dimethyl-adipimidate-dihydrochloride, and 1,5,-2,4 dinitrobenzene; wherein the crosslinker comprises a hetero-bifunctional crosslinker selected from the group consisting of N-hydroxysuccinimidyl 2, 3-dibromopropionate; 1-ethyl-3-[3-dimethylaminopropyl] carbodiimide hydrochloride; and succinimidyl 4-[n-maleimidomethyl]-cyclohexane-1-carboxylate; a nucleic acid molecule comprising a nucleic acid sequence which encodes a polypeptide according to claim 1; a nucleic acid molecule comprising the sequence selected from the group consisting of: (i) the sequence represented by Figure 4 or 6, (ii) a sequence which hybridizes to the sequence of (i) above and which has cytokine receptor modulating activity and (iii) a sequence which is degenerate as a result of the genetic code to the

sequences defined in (i) and (ii) above; a nucleic acid molecule which hybridizes under stringent hybridization conditions to the sequences represented in Figure 4 or 6; a polypeptide encoded by the nucleic acid molecule according to claim 29; a polypeptide according to claim 32 wherein said polypeptide is modified by deletion, addition, and/or substitution of at least one amino acid residue and said modification enhances the antagonistic or agonistic effects of said polypeptide with respect to the inhibition or activation of receptor mediated cell signaling; a vector comprising the nucleic acid molecule of claim 29; a vector according to claim 34 wherein the vector is an expression vector adapted for prokaryotic or eukaryotic gene expression; a vector according to claim 34 wherein the vector further encodes a secretion signal linked to the polypeptide to facilitate purification of the polypeptide; a method to prepare a polypeptide according to claim 1 comprising (i) growing a cell transformed or transfected with a nucleic acid of claim 29 in conditions conducive to the manufacture of the polypeptide and (ii) purifying the polypeptide from the cell or its growth environment; a cell transformed/transfected with the vector of the nucleic acid of claim 29; a pharmaceutical composition comprising the polypeptide of claim 1 and a pharmaceutically acceptable carrier, excipient, or a diluent; a method for treating a disease selected from the group consisting of: GH deficiency [as elected], wherein said method comprising administering to a patient in need thereof a pharmaceutical composition according to claim 43.

Cunningham et al., teach ternary complexes of hGH with their receptors that can act as agonists or antagonists. Agonists comprised of hGH ligands are taught at column 3, lines 36-67 to column 4, lines 1-5. hGH-C-terminal-fusion proteins are taught at column 36, Example 9. Antagonists comprised of hGH ligands are taught at column 8, lines 47-65. Antagonist and agonist ligand variants are taught at column 23, lines 34-52. Therapeutic compositions are taught at column 22, lines 10-67. Cunningham et al., do not teach tandem hGH ligands with polypeptide linkers.

Baumann et al., teaches a covalently cross-linked complex of growth hormone and the growth hormone binding protein linked through a covalent chemical cross-linker (p. 330, Materials and Methods). This polypeptide complex would prevent dimerization of membrane-bound growth hormone receptor and is therefore inherently an antagonist of growth hormone receptor. The polypeptide was injected into rats in a pharmaceutical composition. Baumann et al., further teach that the polypeptide is protected from clearance and degradation by being restricted from access to degradation sites.

Sytkowski et al., teach recombinant fusion proteins, either with or without peptide linkers (Abtract). Sytkowski et al., also teach increased biological activity results from the production of fusion proteins that result in protein multimers (p. 3). Sytowski et al., further teach the construction of a fusion

protein using a peptide linker of 17 amino acids comprising three repeats of the sequence Gly-Gly-Gly-Gly-Ser (p. 53). Sytowski et al., also teach that the N-terminus of one protein can be joined to the C-terminus of the other protein, or vice-versa (p. 9). Sytowski et al., teach a fusion protein with one or more changes to the amino acid sequence (p. 27), isolated RNA (nucleic acid) encoding a fusion protein (p. 58), an isolated pcDNA3.1 *E. coli*/mammalian expression vector containing a nucleic acid encoding the fusion protein (p. 56), transfected COS cells comprising the nucleic acid encoding the fusion protein (p. 57), transformed *E. coli* cells comprising a nucleic acid encoding the fusion protein (p. 56), and an expression vector encoding the fusion protein (p. 15).

Desplancq et al., teaches a linker peptide consisting of 1, 2, 3, 4, 5 or 6 copies of the sequence Gly-Gly-Gly-Gly-Ser (p. 1028).

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to use the multiple ligand binding sites of hGH as taught by Cunningham with a linker peptide taught by Desplancq et al., in the fusion protein taught by Baumann et al. The person of ordinary skill in the art would have been motivated to make that modification because Baumann et al., teaches that the fusion protein polypeptide linker can be any amino acid sequence over three amino acids and Desplancq et al., teaches that this sequence is a commonly used linker sequence (Gly4Ser). The person of ordinary skill in the art would have expected success because Baumann teaches that any amino acid sequence will work as a polypeptide linker and in the absence of evidence to the contrary, the linker taught by Desplancq et al., would be expected to work as well as any other linker.

It would also have been obvious to the person of ordinary skill in the art at the time the invention was made to produce chemically cross linked polypeptide as taught by Baumann et al., recombinantly as a fusion protein as taught by Sytowski et al., with or without a linker, as taught by Sytowski et al. or Desplanq et al., with either protein fused at the N-terminus to the C-terminus of the other protein, and to use any of the nucleic acids or vectors taught by Sytowski et al., in the production of the fusion protein. This includes a sequence identical to SEQ ID NO: 18, which encodes a fusion protein encoding growth hormone and a linker. The person of ordinary skill in the art would have been motivated to make that modification because of the benefit (as taught by Baumann et al.,) of linking growth hormone and the generally applicable teachings of Sytowski et al., that fusion of proteins, with or without linkers, results in increased biological activity, and because recombinant production of the fusion protein would allow for synthesis of the entire fusion protein in one step rather than individual synthesis or purification of each of the components followed by chemical cross-linking of the individual chemical components. Further, the person of ordinary skill in the art would be motivated to use any of the nucleic acids, vectors, or host cells

as taught by Sytowski et al., because Sytowski et al., teach that these nucleic acids, vectors, and host cells can be used for the production of any recombinant fusion protein. The person of ordinary skill in the art would have expected success because Sytowski et al., teach all of the techniques necessary for the recombinant production of fusion proteins and, in the absence of other evidence, one would expect these techniques to work as well for a fusion of growth hormone as with other proteins taught by Sytowski et al.

Conclusion

NO CLAIM IS ALLOWED.

29. A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Cherie M. Woodward whose telephone number is (571) 272-3329. The examiner can normally be reached on Monday - Thursday 9:00am-7:30pm (EST).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached on (571) 272-0961. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

CMW

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